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Homeostatic model assessment indices in evaluation of insulin resistance and secretion in hemodialysis patients

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Background: Some previous observations suggest that insulin resistance and glucose metabolism disturbances are frequent complications of chronic kidney disease. However, there are no conclusive studies on other indices of the effectiveness of insulin action in end-stage renal disease (ESRD) patients, including chronically hemodialysed (HD) ones.


Material/Methods: The groups comprised 33 non-diabetic ESRD hemodialysed patients and 33 healthy controls matched for age, sex, and body mass index (BMI). In both groups, HOMA-%B, HOMA-%S, HOMA-IR indices, and DI were calculated using HOMA1 and HOMA2 as measures of insulin resistance. The indices were also assessed in subgroups divided according to BMI.

Results: Mean fasting plasma glucose concentrations were lower in ESRD patients than in healthy persons (82.4 ± 10.4 vs. 93.9 ± 11.6 , $p=0.001$). Fasting serum insulin concentrations were similar in both groups (median 6.8 vs. 6.0 mU/l, $p=0.698$). HOMA1-%B values were higher in ESRD patients than controls (median 137.1 vs. 81.6, $p=0.002$). HOMA1-%S (median 75.6 vs. 71.5) and HOMA1-IR (median 1.3 vs. 1.4) values were not significantly different ($p=0.264$ and $p=0.189$, respectively). DI1 levels were higher for HD patients than for healthy subjects (median 1.16 vs. 0.53, $p<0.001$). In subgroup analysis, all statistically significant differences were restricted mainly to persons with BMI <25 kg/m². Similar results as for the HOMA1 model were obtained for HOMA2.

Conclusions: 1. HOMA beta-cell function is strongly correlated with HOMA insulin resistance in HD patients. 2. In non-diabetic ESRD hemodialysed patients, the HOMA indices and DI may be useful and important models in interpretation of glucose metabolism disturbances.

Key words: chronic renal failure • insulin resistance • β -cell function • homeostatic model assessment • disposition index

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Background

Insulin resistance (IR) is a frequent complication in the end-stage renal disease (ESRD), including hemodialysed patients (HD), and is a significant risk factor for cardiovascular diseases in this group of patients.

Insulin resistance is already present in the early stages of chronic kidney disease (CKD), even in patients with a normal glomerular filtration rate (GFR) [1]. GFR in the first period of CKD depends on the severity of proteinuria [2]. Disorders of carbohydrate metabolism are also common in patients with ESRD. Some scientists have evaluated IR in patients in various stages of CKD and proved that greater insulin resistance is associated with lower renal function [3]. Renal replacement therapy, which corrects the disorders that affect IR, may reduce IR intensity [4,5]. Some studies on IR concerning patients with ESRD before renal replacement therapy confirm the existence of increased values of indices of IR [6,7].

However, the study of Bastürk and Unsal proved that there was no significant difference in GFR at the end of the study between patients who had or did not have increased IR. Furthermore, HOMA-IR was not significantly different in patients with or without renal failure [8].

There are also no conclusive data on insulin secretion in ESRD. The method of establishing glucose metabolism disturbances in ESRD patients is not clearly defined.

The objective of the present study was to investigate the usefulness of homeostatic model assessment indices of insulin action (HOMA-%B, HOMA-%S, HOMA-IR) as well as disposition index (DI) calculated with 2 methods in ESRD patients without diabetes in comparison to healthy control subjects.

Material and Methods

Analytical procedures and data analysis

The study included 66 patients, aged 50 to 80 years old, hospitalized in the Nephrology Department at the Medical University of Warsaw.

Group I comprised 33 non-diabetic ESRD subjects undergoing haemodialysis (25 men and 8 women) and group II included 33 healthy controls matched for age, sex, and body mass index (BMI). The groups were subdivided by BMI into the following subgroups: <25 (n=15 pairs), 25–30 (n=9 pairs), and >30 (n=9 pairs) kg/m². The cause of ESRD included idiopathic chronic glomerulonephritis in non-diabetic individuals.

Fasting plasma glucose concentrations were assayed by glucose hexokinase (Roche Cobas Integra 800 analyzer). Serum insulin concentrations were determined by IRMA (Immunotech).

HOMA-IR, HOMA-%B, HOMA-%S, and disposition index were calculated by 2 methods: HOMA1 and HOMA2. For HOMA1, the following formulae were used.

$$\text{HOMA-IR1} = [\text{fasting insulin (mU/l)} \times \text{fasting glucose(mg/dl)} \times 0.0555] / 22.5$$

$$\text{HOMA-\%B1} = [20 \times \text{fasting insulin (mU/l)}] / [(\text{fasting glucose (mg/dl)} \times 0.0555) - 3.5]$$

$$\text{HOMA-\%S1} = [1 / \text{HOMA-IR1}] \times 100\%$$

$$\text{Disposition index 1} = (\text{HOMA-\%S1} / 100) \times (\text{HOMA-\%B1} / 100)$$

HOMA-IR2, HOMA-%B2 and HOMA-%S2 were derived using the HOMA calculator (<http://www.dtu.oc.ac.uk>) and disposition index 2 results from multiplication of HOMA-%S2/100 by HOMA-%B2/100.

The study was approved by the Ethics Committee at the Medical University of Warsaw on 20 June 2006 with the amendment made on the 21 October 2009. Informed consent was given by every patient.

Statistical methods

All statistical data are presented as means, standard deviations (SD), and medians. Wilcoxon exact test was used to compare matched groups. The correlation between metabolic variables was assessed by Spearman's rho. A p value of <0.05 was considered statistically significant. The data were analysed using the program SPSS v.18.

Results

The results of fasting glycemia and fasting serum insulin are shown in Table 1 and 2, and the results of HOMA parameters and DI in the ESRD patients and control subjects are presented in Tables 3–5.

Fasting plasma glucose and serum insulin concentrations

Glucose concentrations were significantly lower in ESRD patients compared with healthy subjects (p=0.001). However, this difference was higher in persons with BMI <25 and 25–30 kg/m² (p=0.011 and p=0.078, respectively) than in obese subjects (p=0.359) (Table 1).

Table 1. Fasting plasma glucose concentration in non-diabetic ESRD patients undergoing haemodialysis and healthy control group.

Fasting plasma glucose (mg/dl)		HD	Control group	p-value*
BMI <25.0	Mean ±SD	80.9±9.6	93.9±8.5	0.011
	Median	78.0	95.0	
BMI 25.0–30.0	Mean ±SD	77.6±8.7	92.3±15.6	0.078
	Median	79.0	89.0	
BMI ≥30.0	Mean ±SD	88.8±11.2	95.4±12.6	0.359
	Median	92.0	93.0	
Total	Mean ±SD	82.4±10.4	93.9±11.6	0.001
	Median	79.0	93.0	

* Wilcoxon exact test

Table 2. Fasting serum insulin concentration in non-diabetic ESRD patients undergoing haemodialysis and healthy control group.

Fasting plasma insulin (mU/l)		HD	Control group	p-value*
Total	Mean ±SD	9.0±11.6	8.4±5.9	0.698
	Median	6.8	6.0	

* Wilcoxon exact test

Table 3. Homeostatic model assessment of β-cell function (HOMA1 and 2-%B) in non-diabetic ESRD patients undergoing haemodialysis and healthy control group.

BMI		HOMA1-βC (33 pairs)			HOMA2-βC (29 pairs)		
		HD	Control group	p-value*	HD	Control group	p-value*
<25.0	Mean ±SD	161.4±138.7	88.8±108.5	0.022	114.0±42.3	82.5±49.0	0.042
	Median	132.9	56.0		102.2	67.38	
25.0–30.0	Mean ±SD	276.4±265.6	112.0±70.0	0.027	126.1±47.6	93.0±40.3	0.027
	Median	164.8	83.5		113.8	81.2	
≥30.0	Mean ±SD	202.4±188.7	135.7±54.9	0.496	104.9±30.5	112.2±32.2	0.945
	Median	130.8	109.7		99.3	100.8	
Total	Mean ±SD	203.9±193.1	107.9±86.7	0.002	115.2±40.6	94.0±42.7	0.013
	Median	137.1	81.6		109.3	81.2	

* Wilcoxon exact test.

There was no significant difference between insulin concentrations in ESRD patients and healthy subjects (median 6.8 vs. 6.0 mU/l, p=0.698), irrespective of BMI (Table 2).

Homeostatic model assessment of β-cell function (HOMA1-%B)

The homeostatic model assessment of β-cell function (HOMA1-%B) values were significantly higher in ESRD patients compared with healthy subjects (median 137.1 vs. 81.6, p=0.002).

In subgroups with BMI <25.0 and 25.0–30.0 kg/m², HOMA1-%B values were significantly higher in HD patients compared with healthy subjects (p=0.022 and p=0.027, respectively). In the group with BMI >30 kg/m² there was no significant difference between HD patients and controls (p=0.496) (Table 3).

Similarly, the HOMA2-%B values were significantly higher in ESRD patients compared with healthy subjects (median 109.3 vs. 81.2, p=0.013).

Table 4. Homeostatic model assessment insulin sensitivity (HOMA1-%S) and homeostatic model assessment insulin resistance (HOMA1-IR) in non-diabetic ESRD patients undergoing haemodialysis and healthy control group.

BMI		HOMA1 (33 pairs)			HOMA2 (29 pairs)		
		HD	Control group	p-value*	HD	Control group	p-value*
HOMA-IR	Mean ±SD	2.0±3.0	2.0±1.5	0.189	1.0±0.4	1.1±0.8	0.559
	Median	1.3	1.4		0.9	0.8	
HOMA-S%	Mean ±SD	91.5±66.3	72.9±40.8	0.264	121.9±53.4	121.6±59.9	0.189
	Median	75.6	71.5		107.4	126.4	

* Wilcoxon exact test.

Table 5. Disposition index 1 (DI1) in non-diabetic ESRD patients undergoing haemodialysis and healthy control group.

BMI		DI1 (33 pairs)			DI2 (29 pairs)		
		HD	Control group	p-value*	HD	Control group	p-value*
<25.0	Mean ±SD	1.37±0.88	0.57±0.27	0.005	1.29±0.37	0.99±0.17	0.052
	Median	1.25	0.48		1.32	0.94	
25.0–30.0	Mean ±SD	1.99±1.78	0.73±0.43	0.098	1.42±0.44	1.08±0.46	0.164
	Median	1.16	0.63		1.33	1.13	
≥30.0	Mean ±SD	0.91±0.74	0.58±0.32	0.359	1.10±0.32	0.84±0.33	0.078
	Median	0.55	0.52		0.98	0.74	
Total	Mean ±SD	1.41±1.20	0.62±0.33	<0.001	1.28±0.39	0.98±0.33	0.006
	Median	1.16	0.53		1.29	0.96	

* Wilcoxon exact test.

Homeostatic model assessment of insulin sensitivity (HOMA1-%S) and insulin resistance (HOMA1-IR)

The values of homeostatic model assessment of insulin sensitivity HOMA1-%S (median 75.6 vs. 71.5, $p=0.264$) and insulin resistance HOMA1-IR (median 1.3 vs. 1.4, $p=0.189$) were not significantly different in ESRD patients compared with healthy controls (Table 4).

No statistically significant difference was found for HOMA2-%S ($p=0.189$) and HOMA2-IR ($p=0.559$).

Homeostatic model assessment of disposition index

Disposition index 1 (DI1) (Figure 1) was higher for the whole HD group than for controls (median 1.16 vs. 0.53, $p<0.001$). However, after subgroup analysis, the difference was significant in the group with BMI <25 kg/m² only (median 1.25 vs. 0.48 $p=0.005$) (Table 5).

Disposition index 2 (DI2) was also significantly higher for the HD patients (median 1.29 vs. 0.96, $p=0.006$).

Discussion

IR significantly contributes to the development of carbohydrate metabolism disorders in many diseases, including ESRD patients. Clinically, it is characterized by normal serum insulin concentration associated with abnormal glucose response [9]. IR is associated with prevalent CKD and fast decrease in renal function in elderly patients, whereas co-existing metabolic syndrome predicts the risks of prevalent and incident CKD [10]. DeFronzo et al. claimed that in IR accompanying uremia, the suppressive effect of insulin on gluconeogenesis in the liver or stimulated glucose uptake by hepatocytes is normal [11]. Not all researchers confirm the increase of insulin resistance in patients with CRF. It is indicated in our study as well (Table 2) [12].

The gold standard in evaluating insulin resistance is believed to be the euglycemic clamp method described by DeFronzo et al. [11], which is considered the best technique for insulin resistance assessment because it provides a direct measurement of the whole-body sensitivity to insulin, particularly in

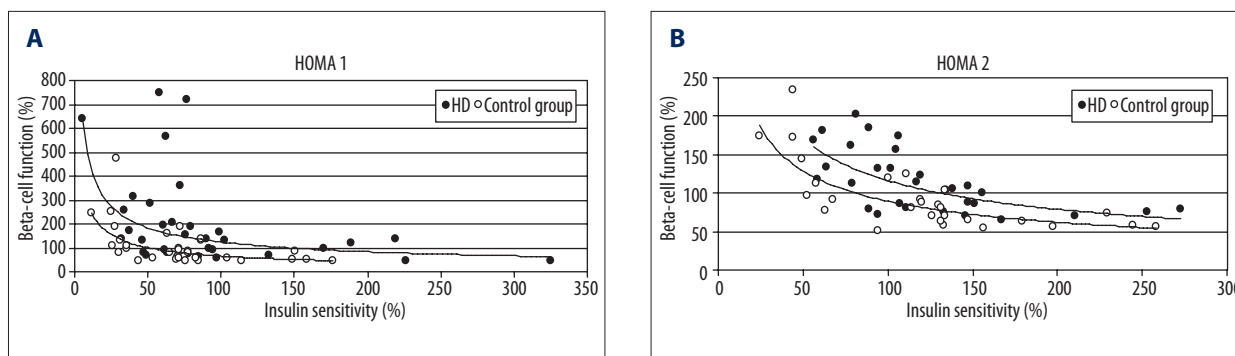


Figure 1. Insulin sensitivity and secretion in HOMA 1 (A) and HOMA 2 (B) models in non-diabetic ESRD patients undergoing haemodialysis and healthy control group.

skeletal muscle. This technique differentiates between peripheral and hepatic insulin resistance because of a direct and accurate measurement [13]. The HOMA-IR test evaluates hepatic rather than peripheral insulin resistance [13]. In CKD, insulin resistance exists mostly as a peripheral mechanism. Some researchers believe that HOMA-IR measurement cannot be the gold standard and is not an accurate method for evaluation of insulin resistance [11,13]. However, a 2000 study by Bonora et al. showed an excellent correlation between euglycemic hyperinsulinemic clamp and HOMA-IR measurements in patients with various degrees of glucose tolerance and insulin sensitivity [14,15]. Shoji et al. showed that HOMA-IR can be alternative technique to assess resistance to insulin in patients with and without renal failure [8,16].

The cause of IR and accompanying chronic renal failure seem to be multifactorial and very complex. The post-receptor signaling pathways of insulin seem to be essential [17]. IR is a derivative of disorders connected with the uremic environment; hence the influence of chronic inflammation, anemia, secondary hyperparathyroidism, and chronic acidosis is stressed. A significant role is attributed to the function of adipose tissue, especially visceral tissue, playing a more important part in secretion of many adipocytokines, which concentrations in renal failure are significantly increased [18]. The following factors determine the existence of IR in CFR patients: excess visceral fat, adipokine deregulation and accumulation, metabolic acidosis, oxidative stress, vitamin D deficiency, decreased physical activity, and accumulation of uremic toxins [19].

Insulin resistance is correlated with serum leptin concentrations and it is strongly correlated with the plasma leptin: adiponectin ratio (LAR) [20,21].

It is widely accepted that ESRD patients may show glucose intolerance due to IR, as the effect of their reduced peripheral sensitivity to the hypoglycaemic activity of insulin. Hemodialysis improves IR observed in uremic patients and, secondarily to this, glycemia could be significantly lowered in ESRD patients

compared to healthy controls, as in our results (Table 1) [5]. In our study, there was no significant difference in fasting serum insulin concentrations between hemodialysed ESRD patients and healthy subjects (Table 2).

Long-term consequences of increased IR include development of diabetes type 2, many vascular disorders, and malignancies. At the moment no single, commonly accepted test for establishing IR in clinical practice is available [22].

Relatively simple, increasingly common, non-invasive alternatives to the clamp technique have been proposed, such as homeostasis model assessment (HOMA) [23]. There is an inverse linear correlation between IR measured by euglycemic hyperinsulinemic clamp and log-transformed IR calculated by HOMA. IR measured by HOMA is considered an alternative method to assess IR in patients with renal failure [13,24]. The results of our study seem to confirm the usefulness of HOMA.

The most popular, commonly accepted method of IR measurement is the HOMA-IR index [25]. There are 2 main methods of calculating HOMA-IR: from the formula and with the calculator (the Oxford method used to calculate HOMA2 is considered to be more accurate [26]). This also applies to other examined indices.

HOMA-%S indicates insulin sensitivity and has various capabilities for assessment. This is the inverse of HOMA-IR multiplied by 100.

The HOMA-%B index is a method for assessing β -cell function from basal glucose and insulin concentrations.

The disposition index is an effect of insulin sensitivity and insulin secretion. It is generally constant for a patient; a change in value seems to be a very sensitive parameter of disturbances in glucose metabolism, as found in our study [27,28]. Regardless of the method of calculation, in our material, the DI in patients on dialysis is higher than in patients without renal failure (Table 5).

HOMA analysis is important in both clinical and epidemiological studies. However, the HOMA-IR (or HOMA-%S) index is usually examined and HOMA-%B and DI are calculated less often. For example, the study by Heald et al. confirmed the usefulness of the HOMA-%B index in a general population of migrants from India [29]. Matthews et al. demonstrated the usefulness of this test for the determination of pancreatic beta-cell function both in diabetic and non-diabetic patients [30]. HOMA-%B has also been used to assess pancreatic function in many other populations [31–34]. It is also useful in predicting the function of beta-cells in time [35].

A correlation of 0.7 was demonstrated between HOMA-%B and metabolic clamp study in assessing the function of beta-cells in patients with diabetes and a correlation of 0.5 to 0.8 with the intravenous glucose tolerance test in non-diabetic and diabetic patients [30,33]. Hermans et al. demonstrated the usefulness of the beta-cell function index in the dynamic CIGMA test (CIGMA-%B) with continuous infusion of glucose [36]. CIGMA-%B provides better discrimination for distinguishing beta-cell function than other tests in patients with normal or impaired glucose tolerance and type 2 diabetes. The intravenous glucose tolerance test did not demonstrate any advantage in quantifying insulin secretion in these patients compared with the model-based HOMA and CIGMA tests.

It has also been demonstrated that the areas under the curve of insulin concentrations, C-peptide, and glucose obtained in the course of the oral glucose tolerance test have greater usefulness for scientists in the evaluation of insulin secretion by pancreatic beta-cells than HOMA-%B [37,38].

The interpretation of HOMA-%B should be simultaneous with the evaluation of HOMA-%S [28].

In our study, HOMA-%B was higher in HD patients than in healthy subjects, regardless of the method of counting. This proves undisturbed pancreatic function in patients with ESRD. On the other hand, there was no difference in HOMA-IR and HOMA-%S between HD and the control group, which may suggest low sensitivity of the examined indices, the actual lack of a difference, or low usefulness of examined tests carried out on an empty stomach (Tables 3 and 4, Figure 1).

The role of overstimulation of the pancreas to produce insulin in CRF is not obvious. Tuzcu et al. analyzed HOMA-%B in

HD and continuous ambulatory peritoneal dialysis (CAPD) patients and found higher values in CAPD than HD or the control group, but similar in HD and the control group [39]. Shehab-Eldin et al. also did not confirm beta-cell dysfunction, despite the fact that the results of this study were similar to ours [36]. Pancreatic beta-cell function was also established in other studies, in non-diabetic and diabetic patients with normal and impaired renal function using HOMA-%B, plasma glucose, and insulin concentrations obtained at fasting or during 75-gram oral glucose tolerance test (insulin sensitivity index), insulinogenic index, first-phase insulin secretion index, and area under the curve of plasma insulin [12]. In non-diabetic patients, there was no difference in insulin secretion between patients with normal and impaired renal function.

The homeostatic responsivity index HOMA-B, derived from basal measurements of insulin and glucose, is a relatively easy and common method of assessment of beta-cell function. The use of C-peptide instead of insulin in HOMA-B has been encouraged to avoid the confounding effect of hepatic insulin extraction. Although HOMA-B is widely used because of its simplicity, it has its limitations because it is assessed under non-stimulated conditions [28]. Dynamic tests seem to be necessary for a precise evaluation of disorders of carbohydrate metabolism in patients with CRF, as well as in elderly patients [41].

Attempts to determine the usefulness and accuracy of HOMA methods are important and were presented in this article. It is significant because these methods are safe, simple, and non-aggravating for the patient [13].

The results of our study can be helpful in choosing the method of assessment of insulin resistance in HD patients.

Conclusions

1. Homeostatic model assessment beta-cell function (HOMA-%B) is strongly correlated with insulin resistance level (HOMA-IR) in HD patients.
2. In non-diabetic and end-stage renal disease patients undergoing hemodialysis, the homeostatic model assessment indices and disposition index may be useful and important models in interpretation of glucose metabolism disturbances.

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